

Patient Safety Tip of the Week

July 21, 2020

Is This Patient Allergic to Penicillin?

We haven't given much attention to the issue of penicillin allergy in our patient safety columns. Penicillin, of course, is one of our oldest antibiotics and has been widely used since the 1950's. Its analogs and second and third generation cousins have been used to treat millions of infections as well as serving as prophylactic agents to prevent infection in surgery and other procedures. In patients who cannot receive penicillins we often have to resort to other antibiotics, leading to antibiotic resistance to those other antibiotics. In addition, use of many of those other antibiotics may lead to unwanted consequences such as C. diff infection. So, good antibiotic stewardship needs to focus not just on antibiotic use, per se, but also on how the issue of penicillin allergy might be impacting antibiotic use.

We have discussed problems with the electronic health record (EHR) that may either lead to inappropriate administration of a penicillin in a patient who is allergic to it, or in the opposite direction, avoiding penicillins in a patient who is not really allergic to them. Our January 2013 What's New in the Patient Safety World column [“More IT Unintended Consequences”](#) gave an example of a patient who was allergic to penicillin developing anaphylaxis after being given ampicillin. The information about the allergy had been entered into part of the EHR that was not linked to the allergy portion of the pharmacy computer system that would have triggered an alert if the allergy had been recognized. On the other hand, our July 2020 What's New in the Patient Safety World column [“Patient Requests for EHR Corrections”](#) noted a scenario where your own electronic health record (EHR) says you are allergic to penicillin but you are not, in fact, allergic to penicillin. Yet, you might at some time in the future be denied appropriate use of penicillins or other antibiotics cross-reacting with penicillin.

So, why is it so important to know whether your patient has a true penicillin allergy? Probably the best example is the patient about to undergo surgery. A study published in Clinical Infectious Disease looked at surgical site infections (SSI's) in over 9000 surgical procedures and found that patients giving a history of penicillin allergy had 50% increased odds of SSI ([Blumenthal 2018](#)). Reason: they received second-line perioperative antibiotics. They were administered less cefazolin (12% vs 92%) and more clindamycin (49% vs 3%), vancomycin (35% vs 3%), and gentamicin (24% vs 3%) compared with those without a reported penicillin allergy. The authors conclude that

clarification of penicillin allergies as part of routine preoperative care may decrease SSI risk.

Some hospitals now include penicillin allergy testing as part of their preoperative patient optimization. In our April 7, 2020 Patient Safety Tip of the Week “[From Preoperative Assessment to Preoperative Optimization](#)” Aronson and colleagues ([Aronson 2020](#)) detailed how they established a comprehensive preoperative assessment and management program to optimize patients for surgery at Duke University Hospital and School of Medicine. Their multidisciplinary group implemented a Preoperative Anesthesia and Surgical Screening (PASS) Clinic to screen patients and to more proactively and efficiently manage modifiable risks at the time a patient’s surgical candidacy is first considered. One of their specific optimization programs was a preoperative penicillin allergy testing clinic,

Interestingly, Kimberly Blumenthal, M.D., author of the study noted previously, says “But just because you were told you had a penicillin allergy, or had one in the past, does not mean you have one now. People with a penicillin allergy history have their allergy disproved with allergy testing more than 90% of the time.” ([Blumenthal 2019](#)). So, confirming or ruling out a penicillin allergy through allergy testing could justify the risk, or potentially avert it by allowing use of beta-lactams. The first step is skin testing for penicillin allergy. Anyone with a positive skin test to penicillin — usually itching, redness, and swelling at the site of the skin prick — is allergic and should avoid penicillin. People who have no reaction to the skin test can then safely undergo the amoxicillin challenge. In that test, the allergist gives the person amoxicillin and observes signs and symptoms for at least one hour. This is done under medical supervision.

In a recent AORN Journal interview, it was noted that beta lactams, the group of antibiotics related to penicillin, are the most widely used antibiotics to prevent surgical site infections ([Sunshine 2020](#)). The author interviews Valeria Fabre, MD, associate medical director of the Antimicrobial Stewardship Program and at The Johns Hopkins Hospital. Dr. Fabre begins by noting the statistic from the Blumenthal study mentioned above. She goes on to note that most people who have a penicillin allergy label are actually not allergic and that, with an appropriate protocol in place, these patients can safely receive that beta-lactam antibiotic at the time of surgery. Sometimes, intolerance of an antibiotic may be erroneously labelled as allergy. For example, isolated diarrhea or headache after an antibiotic more likely represents intolerance and not a true allergy.

Medical records often just include penicillin or one of its relatives under “allergy” without clarification of what the supposed allergic reaction was. In many cases, it was not a true allergy. Dr. Fabre recommends that some simple questions may help differentiate true allergies from other reactions:

- What was the reaction?
- How did it look (if a rash)?
- When did it happen (i.e. at what age)?
- How soon after the antibiotic was given?
- What other antibiotics has the patient had since the reaction?”

She notes what we are most concerned about is the risk of anaphylaxis in a patient with a true penicillin allergy. This needs to be differentiated from a previous reaction that is actually at low risk for anaphylaxis. She gives a great example regarding a rash occurring after administration of a penicillin. She notes that the most common reaction to penicillin or penicillin-related antibiotics is a skin rash that appears usually after two or three days of taking the antibiotic. It's a diffuse rash that may appear over several areas of the body, feels rough to touch, and is usually red. It's called a delayed rash and, though it can be very impressive, it is a benign rash. If the patient takes the same antibiotic, it may not happen again. That's not a rash that will transform into anaphylaxis. It's very important to distinguish that type of delayed rash from an immediate reaction, which usually occurs within a couple of hours after antibiotic administration. This type of rash is hives and can be associated with anaphylaxis. She again emphasizes that after 10 years, 8 out of 10 patients who had a true penicillin allergy will overcome that allergy. Most people think or fear that if they had an allergy it's a lifelong situation—and that's not the case.

Fabre states that, if the patient is having an elective surgery, there's time to assess the patient and determine if the patient can have the recommended beta-lactam for surgical prophylaxis.

She further notes that understanding responses to previous antibiotics may also be helpful. For example, if a patient is allergic to penicillin, there is a 95% chance of being allergic to amoxicillin too. Why? Because those two antibiotics are very similar. But a patient allergic to penicillin is highly unlikely to have a reaction to a third- or a fourth-generation cephalosporin. Knowing that a patient tolerated a cephalosporin in the past can be very helpful.

Some hospitals will have an allergy clinic where they can perform a skin test to confirm the presence or absence of the allergy. Other hospitals will do a test challenge, in which the patient takes a smaller dose of the antibiotic and is observed for reactions. These protocols can be driven by pharmacy, nursing, allergy, physicians, and advanced practitioners based on local experience. Antibiotic recommendations for patients with true contraindications should be developed by a multidisciplinary team, including antibiotic stewardship, infectious diseases or hospital epidemiology and infection prevention, anesthesia, and surgery to ensure appropriate alternatives based on local epidemiology.

Fabre notes that Johns Hopkins has an [antimicrobial stewardship toolkit](#) that includes a section on penicillin allergy:

There are, of course, costs and delays associated with the need for penicillin allergy testing prior to surgery. Recently, Australian researchers developed a **clinical decision rule** to identify low-risk penicillin allergies that potentially do not require penicillin skin testing by a specialist ([Trubiano 2020](#)). They looked at 622 patients who had been allergy-tested to derive the clinical decision rule. Patients who reported a penicillin allergy underwent penicillin allergy testing using skin prick, intradermal, or patch testing

and/or oral challenge (direct or after skin testing). The 4 features associated with a positive penicillin allergy test result on multivariable analysis were summarized in the mnemonic “**PEN-FAST**”: penicillin allergy five or fewer years ago, anaphylaxis or angioedema, severe cutaneous adverse reaction (SCAR), and treatment required for allergy episode. They assigned points for major and minor criteria: allergy event occurring 5 or fewer years ago (2 points), anaphylaxis/angioedema or SCAR (2 points), and treatment required for an allergy episode (1 point). For internal validation, a cutoff of less than 3 points for PEN-FAST was chosen to classify a low risk of penicillin allergy, for which only 17 of 460 patients (3.7%) had positive results of allergy testing, with a negative predictive value of 96.3%. External validation resulted in similar findings.

The authors conclude that PEN-FAST is a simple rule that accurately identified low-risk penicillin allergies that do not require formal allergy testing. The results suggest that a PEN-FAST score of less than 3, associated with a high negative predictive value, could be used by clinicians and antimicrobial stewardship programs to identify low-risk penicillin allergies at the point of care.

Think about the numbers here. For patients who have a “history” of penicillin allergy, which accounts for about 10% of patients undergoing surgery, there is a potential to reduce their risk of incurring a surgical site infection by up to 50% by doing penicillin allergy testing or assessment. There are very few interventions we do that can reduce SSI risk by 50%! We’re surprised more healthcare systems have not begun to incorporate formal penicillin allergy programs into their preoperative assessment programs.

Of course, it’s not just in the surgery patient for whom assessment of the risk for penicillin allergy exists. There are many other infections where treatment with penicillin or other beta-lactam antibiotic would be preferable to other antibiotics.

This also raises the question about how we use our EHR’s to document allergies. In some, someone simply enters the name of a drug into an allergy field. Better EHR’s would prompt for a description of what sort of reaction occurred to that drug. And it reminds us that we need to ensure that such information gets updated in any other IT systems that may not be fully interoperable. Each healthcare organization or practice should also have protocols for who and how EHR data for allergies can be amended so that an inappropriate designation of an allergy does not get perpetuated.

Recent comprehensive reviews of penicillin allergy have appeared in the New England Journal of Medicine ([Castells 2020](#)) and JAMA ([Shenoy 2019](#)).

The Castells review concludes that, in contemporary clinical practice, more than 90% of patients labeled as allergic to penicillin can safely receive the drug. They note that, on average, 8 to 15% of unselected international patients are labeled as allergic to penicillin, meaning that many patients labeled as allergic to penicillin could safely receive it.

The Shenoy review notes that the goals of antimicrobial stewardship are undermined when reported allergy to penicillin leads to the use of broad-spectrum antibiotics that

increase the risk for antimicrobial resistance, including increased risk of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*, or the risk of developing *Clostridium difficile* infection. The authors suggest that direct amoxicillin challenge is appropriate for patients with low-risk allergy histories and moderate-risk patients can be evaluated with penicillin skin testing, which carries a negative predictive value that exceeds 95% and approaches 100% when combined with amoxicillin challenge.

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